Diabetes Mellitus, acute presentation and complications.

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Hyperosmolar Hyperglycemic Syndrome (or State) {HHS}

Hyperosmolar hyperglycemic state (HHS) is one of two serious metabolic derangements that occurs in patients with diabetes mellitus and can be a life-threatening emergency. The condition is characterized by hyperglycemia, hyperosmolarity, and dehydration without significant ketoacidosis. It less common than the other acute complication of diabetes, diabetic ketoacidosis (DKA), and differs in the magnitude of dehydration, ketosis, and acidosis. HHS usually presents in older patients, dogs and cats equally distributed, and carries a higher mortality rate than DKA.

Most patients present with severe dehydration and focal or global neurologic deficits. In as many as one third of cases, the clinical features of HHS and DKA overlap and are observed simultaneously (overlap cases). Based on the consensus statement published by the American Diabetic Association, diagnostic features of HHS may include the following:

- Plasma glucose level of 600 mg/dL or greater
- Effective serum osmolality of 320 mOsm/kg or greater
- Profound dehydration
- Serum pH greater than 7.30
- Bicarbonate concentration greater than 15 mEq/L
- Marginal ketonuria and absent-to-low ketonemia
- Some alteration in consciousness

HHS was previously termed hyperosmolar hyperglycemic nonketotic syndrome, or Hyperosmolar non ketotic syndrome (HONK).

Pathophysiology

Hyperosmolar hyperglycemic state (HHS) most commonly occurs in patients with type 2 diabetes mellitus who have some concomitant illness that leads to reduced fluid intake. Infection

is the most common cause, but many other conditions can cause altered mentation, dehydration, or both. The concomitant illness may not be identifiable.

In patients with a preexisting lack of or resistance to insulin, a physiologic stress such as an acute illness can cause further net reduction in circulating insulin.

The basic underlying mechanism of HHS is a reduction in the effective circulating insulin with a concomitant elevation of counter-regulatory hormones, such as glucagon, catecholamines, cortisol, and growth hormone. Decreased renal clearance and decreased peripheral utilization of glucose lead to hyperglycemia.

Hyperglycemia and hyperosmolarity result in an osmotic diuresis and an osmotic shift of fluid to the intravascular space, resulting in further intracellular dehydration. This diuresis also leads to loss of electrolytes, such as sodium and potassium.

Unlike patients with DKA, patients with HHS do not develop significant ketoacidosis, but the reason for this is not known. Contributing factors likely include the availability of insulin in amounts sufficient to inhibit ketogenesis but not sufficient to prevent hyperglycemia.

Additionally, hyperosmolarity itself may decrease lipolysis, limiting the amount of free fatty acids available for ketogenesis. Also, lower levels of counter-regulatory hormones have been found in patients with HHS compared with those with DKA.

Mortality/Morbidity

The mortality rate is high (10-20%) and usually due to a comorbid illness The mortality rate of HHS increases with increasing age and with higher levels of serum osmolality HHS is more likely in older patients especially those with significant obesity. DKA on the other had is more commonly seen in middle aged patients and most of these patients are in a catabolic state. The catabolic state leads to marked weight loss. Patients with HHS have significant osmolar shifts and are predisposed to cerebral edema or other myelin injury.

- Most patients with hyperosmolar hyperglycemic state (HHS) have a known history of diabetes.
- In 30-40% of cases, HHS is the patient's initial presentation of diabetes.
- HHS usually develops over a course of days to weeks unlike DKA, which develops more rapidly.
- Often, a preceding illness results in several days of increasing dehydration.
- Adequate oral hydration may be impaired by concurrent acute illness (eg, vomiting) or chronic comorbidity (eg, dementia, immobility).

- Patients may have polydipsia, polyuria, weight loss, weakness.
- Patients do not typically exhibit abdominal pain, a complaint that is often noted in patients with DKA.

- A wide variety of focal and global neurologic changes may be present, including the following:
    - Drowsiness and lethargy
    - Delirium
    - Coma
    - Focal or generalized seizures
    - Visual changes or disturbances
    - Hemiparesis
    - Sensory deficits

Physical

Examine the patient for evidence of hyperosmolar hyperglycemic state (HHS), focusing on hydration status, mentation, and signs of possible underlying causes, such as a source of infection.

- Vital signs
    - STAT glucose should be checked immediately and is usually greater than 600 mg/dL.
    - Tachycardia is an early indicator of dehydration; hypotension is a later sign suggestive of profound dehydration due to volume loss secondary to osmotic diuresis.
    - Tachypnea may occur due to respiratory compensation for metabolic acidosis in overlap cases.
    - Assess core temperature rectally.

        - Abnormally high or low temperatures suggest sepsis as an underlying cause.
        - Lack of fever does not rule out infection.
        - Hypothermia is a poor prognostic factor.
    - Hypoxemia can be a concurrent problem affecting mentation.
- General appearance and hygiene may provide clues to the state of hydration, presence of chronic illness, and reduced level of mentation.
    - Examination may reveal altered hydration status (eg, sunken eyes, dry mouth).
    - Cranial neuropathies, visual field losses, and nystagmus may be appreciated, which are symptoms of HHS. They are usually reversible with therapy.

Causes

- In general, any illness that predisposes to dehydration may lead to hyperosmolar hyperglycemic state (HHS). A wide variety of major illnesses may trigger HHS by limiting patient mobility and free access to water.
- A preceding or intercurrent infection is common, but the underlying cause may be difficult to ascertain. Pneumonia and urinary tract infections (UTIs) are the most common underlying causes of HHS.
- Stress response to any acute illness tends to increase hormones that favor elevated glucose levels. Cortisol, catecholamines, glucagon, and many other hormones have effects that tend to counter those of insulin.
- Patients with underlying renal dysfunction and/or congestive heart failure are at greater risk.
- Drugs that raise serum glucose levels, inhibit insulin, or cause dehydration may cause HHS. Examples include the following:
    - Diuretics
    - Steroids
    - Total parenteral nutrition and fluids that contain dextrose

Poor compliance with insulin therapy or diet can result in HHS.

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is an acute, major, life-threatening complication of diabetes. DKA mainly occurs in patients with type 1 diabetes, but it is not uncommon in some patients with type 2 diabetes. DKA is defined clinically as an acute state of severe uncontrolled diabetes that requires emergency treatment with insulin and intravenous fluids. Biochemically, DKA is defined as an increase in the serum concentration of ketones greater than 5 mEq/L, a blood glucose level of greater than 250 mg/dL (although it is usually much higher), blood pH of less than 7.2, and a bicarbonate level of 18 mEq/L or less.

Pathophysiology

Diabetic ketoacidosis (DKA) is a complex disordered metabolic state characterized by hyperglycemia, acidosis, and ketonuria. DKA usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counter-regulatory hormones (ie, glucagon, cortisol, growth hormone, epinephrine). This type of hormonal imbalance enhances hepatic gluconeogenesis, glycogenolysis, and lipolysis.

Hepatic gluconeogenesis, glycogenolysis secondary to insulin deficiency, and counter-regulatory hormone excess result in severe hyperglycemia, while lipolysis increases serum free fatty acids. Hepatic metabolism of free fatty acids as an alternative energy source (ie, ketogenesis) results in accumulation of acidic intermediate and end metabolites (ie, ketones, ketoacids). Ketones include acetone, beta hydroxybutyrate, and acetoacetate.

Progressive rise of blood concentration of these acidic organic substances initially leads to a state of ketonemia. Natural body buffers can buffer ketonemia in its early stages. When the accumulated ketones exceed the body's capacity of extracting them, they overflow into urine (ie, ketonuria). If the situation is not treated promptly, more accumulation of organic acids leads to frank clinical metabolic acidosis (ie, ketoacidosis), with a drop in pH and bicarbonate serum levels. Respiratory compensation of this acidotic condition results in rapid shallow breathing (Kussmaul respirations).

Ketones, in particular beta hydroxybutyrate, induce nausea and vomiting that consequently aggravate fluid and electrolyte loss already existing in DKA. Acetone produces the characteristic fruity breath odor of ketotic patients.

Hyperglycemia usually exceeds the renal threshold of glucose absorption and results in significant glycosuria. Consequently, water loss in the urine is increased due to osmotic diuresis induced by glycosuria. This incidence of increased water loss results in severe dehydration, thirst, tissue hypoperfusion, and, possibly, lactic acidosis.

Typical free water loss in DKA is nearly 100 mL/kg of body weight. The initial half of this amount is derived from intracellular fluid and precedes signs of dehydration, while the other half is from extracellular fluid and is responsible for signs of dehydration.

Hyperglycemia, osmotic diuresis, serum hyperosmolarity, and metabolic acidosis result in severe electrolyte disturbances. The most characteristic disturbance is total body potassium loss. This loss is not mirrored in serum potassium levels, which may be low, within the reference range, or even high. Potassium loss is caused by a shift of potassium from the intracellular to the extracellular space in an exchange with hydrogen ions that accumulate extracellularly in acidosis. A large part of the shifted extracellular potassium is lost in urine because of osmotic diuresis. Patients with initial hypokalemia are considered to have severe and serious total body potassium depletion. High serum osmolarity also drives water from intracellular to extracellular space, causing dilutional hyponatremia. Sodium also is lost in the urine during the osmotic diuresis.

Typical overall electrolyte loss includes potassium, sodium, and chloride. Additional electrolyte losses include magnesium and phosphorous. The combined effects of serum hyperosmolarity, dehydration, and acidosis result in increased osmolarity in brain cells that clinically manifests as an alteration in the level of consciousness.

Mortality/Morbidity

When diabetic ketoacidosis (DKA) is treated properly, it rarely causes any residual effects. The mortality rate of DKA (or HHS) is sometimes dictated by Owner financial commitment. Best results are always observed in patients treated in ICUs during the first 1-2 days of hospitalization.

- Cerebral edema remains the most common cause of mortality. Cerebral edema frequently results from rapid intracellular fluid shifts. Other causes of mortality include severe hypokalemia, hypophosphatemic anemia and comorbid states (eg, pneumonia, renal dysfunction / pyelonephritis)

History

- Insidious increased thirst (ie, polydipsia) and urination (ie, polyuria) are the most common early symptoms of diabetic ketoacidosis (DKA).
- Nausea and vomiting usually occur and may be associated with diffuse abdominal pain.
- Generalized weakness and lethargy is noted.

- Altered consciousness in the form of mild disorientation or confusion is a possible symptom. Although frank coma is uncommon, it may occasionally occur when the condition is neglected or if dehydration or acidosis is severe.
- Symptoms of possible associated intercurrent infection may include fever, dysuria, coughing, malaise, and arthralgia, among others.
- Frequently DKA occurs because patients develop GI signs and then Owners decrease insulin therapy due to anorexia.
- History of rapid weight loss is a symptom in patients who are newly diagnosed with type 1 diabetes.

Physical

- Signs of dehydration - Weak and rapid pulse, dry tongue and skin, hypotension, and increased capillary refill time
- Patient odor - Characteristic acetone odor
- Signs of acidosis - Shallow rapid breathing or air hunger (Kussmaul or sighing respiration), abdominal tenderness, and disturbance of consciousness
    - Although these signs are not usual in all cases of diabetic ketoacidosis (DKA), their presence signifies a severe form of DKA.
    - Emphasizing that no direct correlation exists between the degree of acidosis, hyperglycemia, and the disturbances in the level of consciousness is important.
- Signs of intercurrent illness - urinary tract infection (UTI), pneumonia, and pancreatitis, among others
    - Noticing that the body temperature may be within the reference range or low, even in the presence of intercurrent infection, is particularly important.
    - Search for signs of infection is mandatory in all cases.

Treatment :

All critically ill diabetic patients need to be adequately volume resuscitated prior to definitive therapy. The volume resuscitation is usually based on crystalloid replacement fluid. Sodium levels should be carefully monitored to make sure that sudden changes in sodium do not create cerebral injury. It is imperative in patients with cardiac dysfunction that volume resuscitation does not lead to pulmonary edema or pleural effusion. Cats are especially prone to volume overload due to a higher incidence of occult cardiac disease.

Once appropriate interstitial rehydration has occurred insulin therapy can be considered. Always place a central line for venous sampling access and to facilitate fluid therapy. Humulin R (regular insulin) CRI is the authors choice for treatment. Numerous algorithms are available in the literature for managing a CRI of insulin and serial blood glucose monitoring. The CRI permits dial up or dial down of effective insulin rates. Simultaneously supplemental glucose as substrate can be administered if the patient is still ketotic. Until ketosis is resolved and the patient is eating and drinking well we do not transition to longer acting insulin. Humulin N is still ideal as a twice a day insulin in dogs and Glargine is the long acting insulin of choice in cats. In both cases tight glycemic control is not attempted at the first hospitalization. Based on serial glucoses a conservative dosage of insulin is selected and the patient is discharged.

During the hospitalization phase it is important to evaluate the patient for concurrent diseases. Presence of Cushings disease, pancreatitis, lymphoma, or other illness with potential long term implications can significantly affect the way in which these patients are managed. If the patient has chronic IBD or GI signs, regulation can become more difficult since these patients do not eat in a regular manner. Any comorbidities identified have to be treated either immediately or planned for in the long term management.

Electrolytes and acid base status have to be checked frequently through the hospitalization. Administration of insulin leads to significant transcellular shifts of potassium and phosphorous. Presence of hypomagnesemia can make it very difficult to normalize serum sodium levels. During therapy a drop of phosphorous to below 2 mEq/L can lead to catastrophic anemia secondary to erythrocyte fragility. Refeeding syndrome can contribute to hypophosphatemia and phosphorous supplementation is extremely important.

Long term care: Owner education and compliance is very important in good overall control of diabetes. Inadequate control leads to Owners frustration and euthanasia may results. Almost all dogs with diabetes develop cataracts at some point in time and may need surgical care if retinal function is appropriate. Use of home glucose monitoring protocols whether with interstitial blood glucose monitors or by teaching Owners techniques of ear pricks helps in better glycemic regulation. Alternatively blood glucose curves in hospital or periodic assessment of fructosamine

can give veterinarians a good overview of adequacy of therapy. Veterinary specific insulins have had erratic availability as well as some quality control issues and should only be used with frequent monitoring.